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Drug Metabolism

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Objectives

- Understand why drug biotransformation takes place
- Be able to distinguish Phase 1 (metabolism) and Phase 2 (conjugation) biotransformation
- Appreciate the role of enzyme induction and inhibition for drug biotransformation
- Learn the major CYP enzymes and know at least one clinically relevant substrate for each one

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Why is Understanding Biotransformation Important?

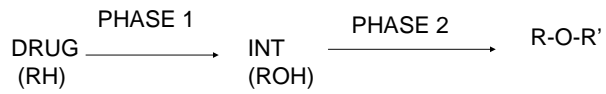
- Major route of drug elimination
- Often activates/inactivates drugs
- May produce toxic products
- Source of between patient variability
- Explains many drug-drug interactions

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Biotransformations

- Two main phases



PHASE 2 – CONJUGATION (SUGARS, SO₄, Acetyl.....)

R-O-R' – USUALLY EXCRETED IN URINE

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Major Enzyme Systems

- Phase 1
 - » Cytochrome P450 (CYP)
- Phase 2
 - » Transferases
 - Glucuronyl-
 - Sulphate-
 - Acetate-

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http://en.wikipedia.org/wiki/Cytochrome_P450

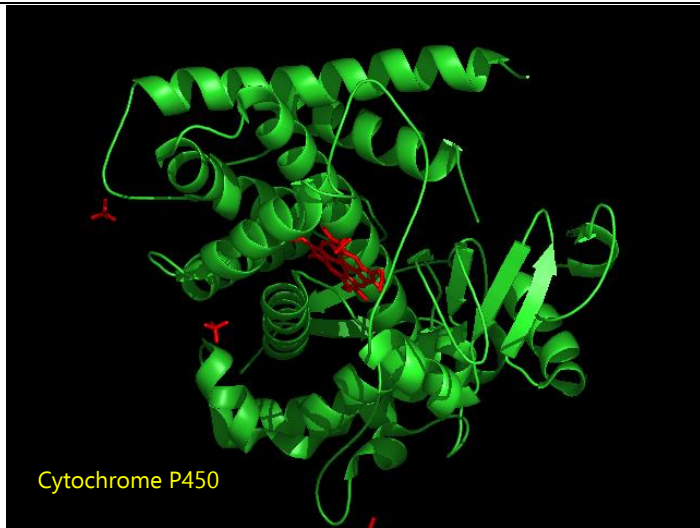
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Cytochrome P450

- Synonyms
 - » CYP
 - » Mixed function oxidase (MFO)
 - » Microsomal P450
- Actions
 - » Over 70% of drugs are metabolized by CYPs
- Location
 - » Gut wall
 - » Liver

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CYP Substrates

| P450 Family | Substrates |
|----------------------|--------------------------------|
| CYP 1,2,3 | Medicines |
| CYP 4,5,8 | Fatty acids, prostaglandins |
| CYP 7,11,17,21,24,27 | Steroids |

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CYP1A2

- Marker Drug ***theophylline***
- Clinically Relevant Drugs
 - » bronchodilator (theophylline)
- Drug Interaction
 - » tobacco, green veges, BBQ (inducer)
 - » cimetidine (inhibitor)
- Ethnicity
 - » ?

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CYP2E1

- Marker Drug ***ethanol***
- Clinically Relevant Drugs
 - » analgesic paracetamol (-> NAPQI)
- Drug Interaction
 - » ethanol (inducer)
- Ethnicity
 - » ?

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CYP2C9

- Marker Drug ***s-warfarin***
- Clinically Relevant Drugs
 - » anticoagulant (warfarin)
- Adverse Event Risk
 - » Lower dose and increased bleeding risk
- Ethnicity
 - » Caucasian 25%
 - » Asian 1%
 - (% with variant alleles and lower CL)

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“CYP2C9 variants with reduced metabolizing ability were less frequent in Japanese compared to the other two populations.”
 Takahashi H, Wilkinson GR, Nutescu EA, Morita T, Ritchie MD, Scordo MG, Pengo V, Barban M, Padrini R, leiri I, Otsubo K, Kashima T, Kimura S, Kijima S, Echizen H. Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population differences in maintenance dose of warfarin in Japanese, Caucasians and African-Americans. Pharmacogenet Genomics 2006; 16: 101-10.

| | Japanese | Caucasian |
|-----------|----------|-----------|
| CYP2C9 | | |
| *2 C430T | 0.000 | 0.133 |
| *3 A1075C | 0.035 | 0.056 |
| Total | 3.5% | 18.9% |

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CYP2C19

- Marker Drug ***s-mephenytoin***
- Clinically Relevant Drugs
 - » acid-pump inhibitor (omeprazole)
- Therapeutic Benefit
 - » Cure of GORD 86% in poor metabolizers, 46% in homozygous extensive metabolizers of lansoprazole
- Drug Interaction
 - » Decreased effectiveness of clopidogrel (a prodrug), an anti-platelet agent, when combined with omeprazole (CYP2C19 inhibitor)
- Ethnicity (% with low clearance)
 - » Caucasian 4%
 - » Asian 20%

©NHG Hoford, 2017, all rights reserved. GORD=Gastro Oesophageal Reflux Disease

[11/17/2009]

FDA is alerting the public to new safety information concerning an interaction between clopidogrel (Plavix), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC), a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced.

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant use of drugs that inhibit CYP2C19, including omeprazole (Prilosec), esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine

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CYP2D6

- Marker Drug ***debrisoquine***
- Clinically Relevant Drugs
 - » tricyclic-antidepressants (amitriptyline)
 - » beta-blockers (metoprolol)
 - » prodrug analgesics (tramadol, codeine)
- Drug Interaction
 - » fluoxetine, quinidine (inhibitor)
- Ethnicity (% with low clearance)
 - » Caucasian 7%
 - » Asian 1%

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CYP3A4

- Marker Drug ***simvastatin***
- Clinically Relevant Drugs
 - » HMG-CoA reductase inhibitor (simvastatin)
 - » protease inhibitor (anti-HIV) (lopinavir)
 - » immunosuppressant (cyclosporine)
- Drug Interaction
 - » ketoconazole, grapefruit juice (inhibitor)
 - » lopinavir with ritonavir for improved effect
 - » St John's Wort (inducer)
- Ethnicity
 - » ?
- *No recognized polymorphism*



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30% of medicines are metabolized to with CYP3A4/5 as the major pathway Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology & Therapeutics. 2013;138(1):103-41.

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CYP Activity

- Induction
 - » Increased activity
 - » Many substances can induce
 - E.g. tobacco smoke induces CYP1A2
- Inhibition
 - » Decreased activity
 - » Usually competitive
 - E.g. grapefruit juice inhibits CYP3A4 (in gut)

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Clinical Applications

- Drug Interaction Awareness
- Dose Individualization
 - » Needs
 - Phenotype
 - Target Concentration Intervention
 - or
 - Genotype
 - Not widely available (yet)

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